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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,570	05/04/2007	Nicolas Zackes Rudinger	630196.401USPC	7112

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,570	RUDINGER ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/25/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-9 and 14-34* is/are pending in the application.

4a) Of the above claim(s) *6-9 and 28-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 6-9, 14-27, 33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/4/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's cancellation of claims 3-5, 10-13, and amendment of claim 17, in the paper of 9/25/2009, is acknowledged. Claims 1-2, 6-9, 14-34 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1, 2, 6-9, 14-27, 33 and 34, drawn to a family A DNA polymerase and a kit comprising a family A polymerase in the paper of 9/25/2009, is acknowledged. The traversal is on the ground(s) that applicants disagree with the assertion that there is no special technical feature that links the three inventions. Applicants submit that the claimed family A polymerase mutant is novel and unobvious. Further applicants argue that Minnick et al. does not teach or suggest a family A DNA polymerase as claimed with a substitution at position Q879.
Applicants complete traversal is acknowledged and has been carefully considered, although not found persuasive on the basis that applicants claims are not determined to be novel and unobvious as further discussed below under the rejection under 112 second paragraph and the rejection based upon the teachings of Minnick et al. Briefly, applicants recitation of a mutation position at Q879, is interpreted as a limitation of the referred to Klenow fragment thereof to which the mutant activity is compared not a limitation of the claimed mutant itself. Thus given this interpretation, applicant's claims are not novel and nonobvious.

Claims 6-9 and 28-32 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosure statement filed on 5/4/2007, is acknowledged. Those references considered have been initialed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 14-27, 33 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (2, 14-27, 33 and 34 dependent on) is indefinite in that it is confusing in the recitation "... at least the amino acid residue Q879 has been replaced by a lipophilic amino acid residue." This recitation is indefinite in that it is unclear if it is applicant's intent that this recitation describe the claimed family A DNA polymerase mutant or the corresponding wild type polymerase or a Klenow fragment thereof. In the interest of advancing prosecution this recitation has been given its broadest reasonable

interpretation and is interpreted as if it is describing the referred to wild type or Klenow fragment thereof. Amendment and/or clarification is requested to clearly define applicants claimed polymerase.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 14-27, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 14-27, 33 and 34 are directed to all possible family A DNA polymerases which have a modified motif C sequence and an enhanced mismatch discrimination as compared to a corresponding wild type polymerase, or a Klenow fragment thereof, wherein in the motif C sequence QVH in positions 879-881, based on the E. coli DNA polymerase Klenow fragment shown in SEQ ID NO: 2, at least the amino acid residue Q879 has been replaced by a lipophilic amino acid residue (See also above rejection under 112 second paragraph).

The specification, however, only provides the representative species of Taq and E. coli DNA polymerase mutants encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these family

A DNA polymerases by any identifying structural characteristics or properties other than the activities recited in claims 1, for which no predictability of structure is apparent (See also above rejection under 112 second paragraph). While applicants have functionally defined the claims in terms of the result of a motif C modification of a family A DNA polymerase, the claims are not limited structurally in any way, such that since the claims are drawn to a family A DNA polymerase which has been modified, the claims no longer have any structural limitations. Given this lack of species representative of such an unlimited genus of modified DNA polymerases, as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 2, 14-27, 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a family A DNA polymerase comprising the amino acid sequence of SEQ ID NO:2, in which the amino acid residue at position Q879 has been replaced with a lipophilic amino acid residue, does not reasonably provide enablement for any family A DNA polymerases which has a modified motif C sequence and an enhanced mismatch discrimination as compared to a corresponding wild type polymerase, or a Klenow fragment thereof, wherein in the motif

C sequence QVH in positions 879-881, based on the E. coli DNA polymerase Klenow fragment shown in SEQ ID NO: 2, at least the amino acid residue Q879 has been replaced by a lipophilic amino acid residue (See also above rejection under 112 second paragraph). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1, 2, 14-27, 33 and 34 are so broad as to encompass any family A DNA polymerases which has a modified motif C sequence and an enhanced mismatch discrimination as compared to a corresponding wild type polymerase, or a Klenow fragment thereof, wherein in the motif C sequence QVH in positions 879-881, based on the E. coli DNA polymerase Klenow fragment shown in SEQ ID NO: 2, at least the amino acid residue Q879 has been replaced by a lipophilic amino acid residue (See also above rejection under 112 second paragraph). The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of enzymes broadly encompassed by the claims, including all

modified family A DNA polymerase enzymes and variants thereof. The claims rejected under this section of U.S.C. 112, first paragraph, place minimal if any structural limits on the claimed modified polymerases. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that family A DNA polymerase comprising the amino acid sequence of SEQ ID NO:2, in which the amino acid residue at position Q879 has been replaced with a lipophilic amino acid residue.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any modified family A DNA polymerase

because the specification does not establish: (A) regions of the protein structure which may be modified without effecting polymerase and mismatch discrimination activity; (B) the general tolerance of family A DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a family A DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the polymerase and mismatch discrimination activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the claimed polymerase and mismatch discrimination activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any family A DNA polymerases which has a modified motif C sequence. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of

those polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 14, 15, 17-25, 27, 33, 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Minnick et al. (Journal of Biological Chemistry, Vol 274, No. 5, pp 30676, 1999, See IDS).

Minnick et al. (Journal of Biological Chemistry, Vol 274, No. 5, pp 30676, 1999) teach a number of family A DNA polymerase mutants including those which have a modified motif C sequence and an enhanced mismatch discrimination as compared to the corresponding wild type polymerase, or a Klenow fragment thereof, wherein in the motif C sequence QVH in positions 879-881, based on the E. coli DNA polymerase Klenow fragment shown in SEQ ID NO: 2, at least the amino acid residue Q879 has been replaced by a lipophilic amino acid residue (See above rejection under 112 second paragraph).

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
1/3/2003

/Richard G Hutson/
Primary Examiner, Art Unit 1652